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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,745	CORY ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,9,12-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,9,12-18 and 20* is/are rejected.

7)☒ Claim(s) *1,3,9,12-18 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03/15/00* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 09/13/2004 has been entered. Claims 2,4-8,10,11 and 19 have been cancelled. Claims 1,3,9,12-18 and 20 have been amended, are pending and under consideration in the instant office action.

Specification

The objection to the specification is withdrawn in light of Applicant's amendments to the Brief Description of the Figures.

Claim Objections

Claims 1,3,9,12-18 and 20 are objected to as being drawn to non-elected subject matter. Claims 1,3,9,18 and 20 are drawn to animals that are not genetically modified (non-elected groups I and IV). Claims 1,3,9,12-18 and 20 encompass disruption of non-endogenous bcl-w genes (Non-elected groups II,IV and V). Claims 14 and 16 are drawn to introduction of an antisense molecule, which is subject matter of non-elected Invention II. Claims are not limited to the elected invention which is a genetically modified non-human animal having reduced levels of Bcl-w protein as an effect of a genetically modified, endogenous bcl-w gene.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of claims 1-3,9,12,13 and 18-20 is withdrawn in light of Applicant's addition of the term "non-human" to the claims.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1,3,9,12-18 and 20 under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement is maintained. The rejection is maintained as it relates to reduced levels of any protein with at least 47% similarity to the mouse Bcl-w protein described in the specification.

Applicant has argued that the present application adequately describes nucleotide sequences having at least 47% similarity to SEQ ID NO:3 and amino acid sequences having the same similarity to the protein of SEQ ID NO:4 as well as those nucleic acids capable of hybridizing to SEQ ID NO:3. In support of this Applicant argues that mice with a disrupted bcl-w gene fail to undergo productive spermatogenesis (page 9, paragraph 2). Applicant argues that the prior art discloses genes encoding proteins with 47% similarity to SEQ ID NO:4 and cites Ralston Purina Co. v. Far-Mar-Co. Inc in arguing that disclosure taken with the knowledge of those skilled in the art may be sufficient support for the claims (page 10 of Applicant's response).

In response, the question is not to whether the skilled artisan can envision nucleic acid sequences encoding proteins with 47% homology to the mouse Bcl-w set forth by SEQ ID NO:4. The question is whether these proteins will have the same function as SEQ ID NO:4 and will, if expressed at reduced levels, cause a failure of productive spermatogenesis in non-mouse species of animal or birds. In addition to the issue of the metes and bounds of the claim discussed below under 35 USC 112, 2nd paragraph, at the most basic level, the specification fails to provide the

description necessary to convey that Applicant was in possession of the claimed animal that when expressing reduced levels of an endogenous bcl-w gene, the animal fails to undergo spermatogenesis. Bcl-w is expressed in a wide variety of tissues, for example hematopoietic tissues, and is known to be involved in cell survival. However, as reported in the specification, the hematopoietic tissues are unaltered in the genetically modified mice lacking bcl-w expression. Other bcl-w homologs, falling within the claimed 47% homology, such as bcl-2, exhibit different phenotypes including lymphocytopenia (see page 2 of the specification). The specification provides description of a mouse lacking a specific gene function, bcl-w, not a homolog or ortholog thereof, exhibits the inability to produce sperm. Based on these general teachings, the description provided by the instant specification is not adequate to demonstrate possession of any other species of animal with reduced levels of any bcl-w homolog with at least 47% homology that fails to undergo spermatogenesis as a result of the altered expression. Furthermore, the claims are so broad as to encompass species A with a decreased level of any protein with 47% homology to SEQ ID NO:4, even proteins from species B. The claims encompass a mouse with decreased expression of bcl-2. Clearly, these embodiments of the claims are not described in the specification.

Claims 1,3,9,12-18 and 20 are rejected, because the specification, while being enabling for a transgenic male mouse whose genome comprises a homozygous disruption in the nucleotide sequence encoding Bcl-w as set forth by SEQ ID NO:3, wherein the mouse exhibits an incapacity for spermatogenesis does not reasonably provide enablement for the other animals encompassed by the claims. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection set forth on pages 7-13 of the previous office action is maintained for reasons of record.

Applicant's arguments have been fully considered and are not found persuasive. First, Applicants have added the limitation of "wherein said bcl-w protein comprises an amino acid sequence set forth in SEQ ID NO:4 or is an amino acid sequence having at least about 47% similarity thereto..." The relevance of this amendment with respect to the rejection is unclear and Applicant fails to provide any context clarifying the issue of which aspect of the rejection the limitation is addressing (see page 13, paragraph 2 of Applicant's response).

Second, Applicants observe that female mice homozygous for a deletion of bcl-w are fertile and heterozygous mice are normal (page 13, paragraph 3 of Applicants' response). However, despite this observation, Applicant's have failed to limit the claimed mice to homozygous mice (refer to aspect #2 on pages 8-10 of the previous office action). Therefore, while Applicants have limited the claims to male mice, the claims continue to encompass heterozygous mice and this aspect of the rejection is maintained.

Third, Applicant points to the definition of mutation in the specification at page 14, lines 9-18. The specification defines "mutation" as "used in its broadest sense and includes a single or multiple nucleotide substitution, deletion and/or addition to bcl-w or to a region controlling bcl-w expression.....For convenience, it is also used to cover reduced levels of functional Bcl-w such as in the case of the administration of an antagonist of Bcl-w or if antisense molecules are used to induce a transient reduction in Bcl-w levels". Applicant argues that the specification teaches how to generate a mutation that results in substantially reduced levels of Bcl-w protein.

Applicant continues by arguing that the teaching of the present invention, combined with the techniques well-established in the art, can readily make the transgenic animals with a mutant bcl-w gene resulting in ha reduced capacity for spermatogenesis.

Claims 1,3 and 9 fail to recite the word mutation and are not necessarily even genetically modified. Claims 13-17 are drawn to genetically modified animals but do not recite the word mutation. Applicants fail to point out the specific relevance of their argument with respect to the definition of the term "mutation". It is assumed that Applicants reference this definition in response to aspect #3 of the rejection set forth on pages 10-11 of the previous office action. This aspect of the rejection is with respect to the breadth of the claims encompassing any type of bcl-w mutation. As set forth in the previous office action, the specification teaches making two different bcl-w alleles that lack the 5' two-thirds of the coding region (page 22, lines 5-28). The specification teaches that neither bcl-w RNA or protein are made (page 22, line 31). Thus, the mice described in the specification are complete nulls for bcl-w. The specification provides no teaching with respect to the structure and function of the bcl-w gene or protein that would allow the skilled artisan to determine how to merely reduce levels of the Bcl-w protein as claimed. Merely contemplating such disruptions in the definition of the term "mutation" is not sufficient to enable the skilled artisan to make an animal with reduced levels of Bcl-w protein other than complete absence. The skilled artisan would have to perform undue experimentation to determine what sorts of mutations would result in a reduction of Bcl-w protein and whether this reduction would be sufficient to cause the claimed spermatogenic phenotype. Therefore, this aspect of the rejection is maintained for reason of record.

Finally, Applicant refers to Genentech. Inc. v. Novo Nordisk, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), cert. denied, 522 U.S. 963 (1997) in stating that a specification only needs to "supply the novel aspects of an invention in order to constitute adequate enablement." Applicant states that, based on the teaching of the present application, those skilled in the art can make a transgenic animal as claimed without undue experimentation (see page 14, paragraph 2).

In response, Applicant has failed to supply novel aspects of the invention and undue experimentation is required to implement the claimed invention on a number of levels. For example, as set forth above, the specification fails to demonstrate how to reduce levels of Bcl-w to any degree other than a null. It is not apparent to the skilled artisan how to reduce levels of Bcl-w protein other than in making a null allele by homologous recombination at the endogenous bcl-w gene. Further experimentation would be necessary to determine how to alter the 5'UTR, degradation rate, translational efficiency, transcriptional efficiency etc. to determine how to reduce levels of Bcl-w protein. Furthermore, the elected invention is drawn to genetically modifying the endogenous Bcl-w gene in any species of non-human animal or avian. Applicant's failed to address this aspect of the rejection as set forth on page 8 of the previous office action. It is not known in the art how to target a gene disruption in any species of animal other than mouse. Therefore, it is maintained that the instant specification is not enabling for any non-mouse species of animal as claimed and it is further maintained in response top Applicants argument with respect to Genentech. Inc. v. Novo Nordisk, that the novel aspects of the invention are not supplied and that undue experimentation is, in fact, necessary to implement the invention as claimed.

It appears that Applicant has failed to address aspect #4 of the enablement rejection set forth on pages 11-12 of the previous office action. The claims continue to encompass chimeric animals. This aspect of the rejection is maintained for reasons of record.

It appears that Applicant has failed to address aspect #5 of the enablement rejection set forth on pages 12-13 of the previous office action. The claims continue to encompass any reduced level of spermatogenesis while the specification supports a complete incapacity for spermatogenesis, as the mice were "devoid" of sperm (page 24, line 8). This aspect of the rejection is maintained for reasons of record.

The rejection with respect to mutation of the bcl-w gene on chromosome 14q11 is withdrawn as Applicant has cancelled the claim.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following aspects if the rejection of the claims under 25 U.S.C. 112, 2nd paragraph are withdrawn:

The rejection of claims 1,2,3 and 9 for use of the term "and/or" and the phrases "the protein associated with Bcl-w" and "induce or facilitate" and "reduced capacity" is withdrawn in light of Applicants' amendments to claim 1 and cancellation of claim 2.

The rejection of claims 3,9,12 and 13 for recitation of "capable of" in claims 3 and 12 is withdrawn in light pf Applicants' amendment to the claims removing the terminology.

The rejection of claim 3 for use of the phrase "a nucleotide sequence having at least about 47% similarity thereto" is withdrawn in light of the amendment to the claim indicating nucleic acid identity, not similarity.

The rejection of claim 3 for use of the term "and/or" is withdrawn in light of the amendment to the claim .

The rejection of claims 16-18 are withdrawn in light of Applicant's amendments to the claims.

The following aspects of the rejection under 35 USC 112, 2nd paragraph are maintained:

The rejection of claims 3 and 12 and claim 1 as amended is maintained with respect to the use of the phrase "At least about". Applicant argues that the meaning of the term is clear to those skilled in the art. In response, it is maintained that the phrase is unclear because the metes and bounds of the phrase are not clear. Applicant refers to Ex parte Eastwood which states that "Descriptive "about" is not indefinite inasmuch as its meaning is not broad and arbitrary; rather, term is clear and flexible and is similar in meaning to terms such as "approximately" or "nearly." However, the claims recite "at least about" and it is not clear if the phrase is including amounts under 47% (i.e.46%) because of the use of the term "at least". It is also unclear if "about" limits the upper metes and bounds to amounts "approximately" or "nearly" 47% (i.e. 48%). Claim 13 depends from claim 12.

The rejection with respect to the term "substantially " in claims 14 and 20 is maintained. Applicant compares the use of "substantially incapable" of claim 14 to "substantially increased" which was held to be clear by the court (In re Mattison). In response, the term "incapable" is definite and means not capable. It is unclear how something can be "substantially" not capable.

Something is either capable or it is not capable. "Substantially increase", however, means to increase by a substantial amount rather than some unsubstantial or insignificant amount. Therefore, it is held that In re Mattison does not apply to the instant rejection. The term "substantially" in claim 20 is also indefinite because it refers to an amino acid sequence being substantially identical, however, the metes and bounds of what would be substantially identical are unclear. It isn't known and is not defined by the specification what level of identity or similarity is necessary for a sequence to be substantially identical, especially in light of the fact that a single amino acid change can alter protein function. Claims 15-17 depend from claim 14.

The following new grounds of rejection are necessitated by amendment:

Claim 1 is unclear because it reads on a modified animal that is not necessarily genetically modified. The claim ends with a comparison of the capacity of the claimed modified animal to a wild-type animal to undergo spermatogenesis. The term "wild-type" refers to the genetic composition of the animal. Use of this term for comparison to the modified animal indicates that the claimed animal is not genetically wild-type; however, genetic modification is not required by the claim. Clarification is necessary. Claims 3 and 9 depend from claim 1.

Claim 1 is also unclear as written. For example, it is unclear if the claim is meant to encompass a modified non-mouse species that exhibits reduced levels of any protein having an amino acid sequence with at least 47% similarity to mouse SEQ ID NO:4, including mouse Bcl-w and other protein not endogenous to that species, or to a non-mouse species A that exhibits reduced levels of the species A homolog of mouse bcl-w wherein the homolog encodes a protein that is at least 47% similar to the mouse Bcl-w protein. It is assumed that Applicant is intending

to claim reduced levels of expression of the respective bcl-w homolog for each species of animal encompassed by the claim.

Claim 13 is unclear because it reads "A genetically male non-human modified animal". It is unclear if the claim is referring to a genetically male animal that is modified in a non-genetic manner as encompassed by claims 1,3, and 9 or if the claim contains a typographical error and is supposed to read "A genetically modified male-nonhuman animal".

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
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